514 Rec'd PCT/PTO 11 JAN 2000

FORM PTO-1390 (REV 11-98)	U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER 423-54
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U S APPLICATION NO (If known, see 37 C F R 1 5) 09/462633 Unassigned
INTERNATIONAL APPLICATION NO. **PCT/JP99/02098**	INTERNATIONAL FILING DATE **20 April 1999**	PRIORITY DATE CLAIMED 20 April 1998

TITLE OF INVENTION

STABILIZED COMPOSITION COMPRISING A BENZIMIDAZOLE TYPE COMPOUND

APPLICANT(S) FOR DO/EO/US

UKAI, Koji, et al

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

A copy of the International Application as filed (35 U.S.C. 371(c)(2)).

a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
b. ☒ has been transmitted by the International Bureau.
c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).

☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).

a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
b. ☐ have been transmitted by the International Bureau.
c. ☐ have not been made; however, the time limit for making such amendments has **NOT** expired.
d. ☐ have not been made and will not be made.

☐ A translation of the amendments to the claims under PCT Article 19 (U.S.C. 371(c)(3)).

☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. To 16. Below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☒ Other items or information. PTO-1449 and International Search Report

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U.S. APPLICATION NO (If known, see 37 C.F.R. 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/462633 Unassigned	PCT/JP99/02098	423-54

17. ☒ The following fees are submitted:

	CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5):	
-- Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $970.00	
-- International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $840.00	
-- International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2) paid to USPTO $690.00	
-- International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) $670.00	
-- International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) $96.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 840.00
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE			
Total Claims	**15**	-20 =	0	X	$18.00	$	0.00
Independent Claims	**3**	-3 =	0	X	$78.00		0.00
MULTIPLE DEPENDENT CLAIMS(S) (if applicable)				+$260.00		$	0.00
TOTAL OF ABOVE CALCULATIONS =						$	**970.00**
Reduction by ½ for filing by small entity, if applicable. A Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).							0.00
SUBTOTAL =						$	**970.00**
Processing fee of $130.00, for furnishing the English Translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +							0.00
TOTAL NATIONAL FEE =						$	**970.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +						$	0.00
Fee for Petition to Revive Unintentionally Abandoned Application ($1,210 – Small Entity Fee = $605)						$	0.00
TOTAL FEES ENCLOSED =						$	**970.00**
						Amount to be: refunded	$
						charged	$

a. ☒ A check in the amount of $970.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 14-1140 in the amount of $_____ to cover the above fees. A duplicate copy of this form is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-1140. A duplicate copy of this form is enclosed.

d. ☐ The entire content of the foreign application(s), referred to in this application is/are hereby incorporated by reference in this application.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

NIXON & VANDERHYE P.C.
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SIGNATURE

Arthur R. Crawford
NAME

25,327 January 11, 2000
REGISTRATION NUMBER Date

394251

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

UKAI, Koji, et al

Atty. Ref.: **423-54**

Serial No. **Unassigned**

Group: **Unknown**

Filed: **January 11, 2000**

Examiner: **Unknown**

For: **STABILIZED COMPOSITION COMPRISING A BENZIMIDAZOLE TYPE COMPOUND**

* * * * * * * * * * *

January 11, 2000

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

PRELIMINARY AMENDMENT

Prior to calculation of the filing fee and in order to place the above identified application in better condition for examination, please amend the specification and claims as follows:

IN THE SPECIFICATION

Page 12, line 2, delete the comma after "acid)" and insert -- and/or --.

Page 19, line 14, delete "As" and insert -- The smaller the average of the particle diameter of the crospovidone was, the smaller the ratio of the swelling of the tablets became. Therefore, as --.

Page 19, lines 15 and 16, delete "the ratio of the swelling of the tablets is decreased. Therefore,".

Page 20, line 1, after "analogue" insert -- (impurities) --.

Page 21, line 4, after "analogue" insert -- (impurities) --.

Page 23, line 1, delete "active" and after "granules" and before the period insert -- containing sodium rabeprazole --.

IN THE CLAIMS

Claim 13, lines 1 and 2, change "any of claims 9 to 11" to -- claim 1 --.

REMARKS

The above amendments are made to clarify the specification and to place the claims in a more traditional format.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____

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Description

Stabilized composition comprising a benzimidazole type compound

Field of the Invention

The present invention relates to pharmaceutical preparations of the solid dosage form for internal use comprising benzimidazole type compounds or alkali metal salts thereof.

Prior Art

A benzimidazole type compound or an alkali metal salt thereof has a strong inhibitory action on the so-called proton pump, and it is widely used as a therapeutic agent for stomach ulcer, duodenal ulcer etc., by inhibiting gastric acid secretion. On the other hand, the benzimidazole type compound is chemically very unstable, so various measures have been invented for pharmaceutical manufacturing thereof. For example, JP-A 62-277322 discloses a process for producing a stabilized pharmaceutical composition comprising a basic inorganic salt of magnesium and/or calcium incorporated into a benzimidazole type compound, and JP-A 62-258320 discloses an oral pharmaceutical preparation prepared by incorporating an alkali compound into the portion of a core containing a benzimidazole type compound, then coating it with fillers for tablets soluble in water or rapidly degradable with water or

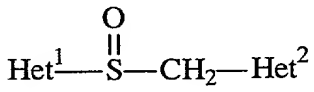
with a polymeric and water-soluble film-forming compound, and further coating it with an enteric coating.

However, the stability of such pharmaceutical preparations is still insufficient even by the prior art described above, so there is demand for further improvements. That is, the object of the present invention is to further stabilize a pharmaceutical preparation of the solid dosage form for internal use comprising a benzimidazole type compound.

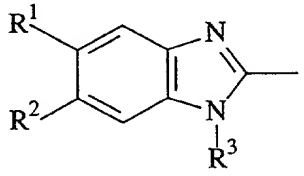
Disclosure of the Invention

The present invention relates to a composition comprising at least one selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone incorporated into a benzimidazole type compound represented by the structural formula (formula 1) below or an alkali metal salt thereof.

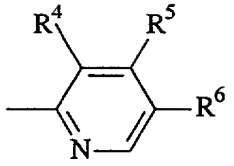
Formula 1



In the formula 1, Het^1 is



Het^2 is



R^1 and R^2 are the same as or different from each other and are selected from a hydrogen, a methoxy and a difluoromethoxy, R^3 is selected from a hydrogen and a sodium, R^4, R^5 and R^6 are the same as or different from each other and are selected from a hydrogen, a methyl, a methoxy, a methoxypropoxy and a trifluoroethoxy.

Further, the present invention relates to a pharmaceutical preparation comprising a core which comprises at least one selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone incorporated into a benzimidazole type compound represented by formula 1 or an alkali metal salt thereof, is coated with an enteric coating.

Further, the present invention relates to a pharmaceutical preparation comprising a core which comprises at least one selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone incorporated into a benzimidazole type compound represented by formula 1 or an alkali metal salt thereof, coated with an intermediate coating and further with an enteric coating.

The present invention further relates to a pharmaceutical preparation comprising a core which comprises at least one selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone incorporated into a benzimidazole type compound represented by formula 1 or an alkali metal salt thereof, coated with an intermediate coating, further with an enteric coating and then with a moisture resistant coating.

The present invention relates to a pharmaceutical composition comprising (A) benzimidazole type compound represented by formula 1 or an alkali metal salt thereof and (B) at least one substance selected from the group consisting of sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone.

Further, the present invention relates to a pharmaceutical preparation comprising a core consisting of the composition described above and an enteric coating. The pharmaceutical preparation may comprise an intermediate coating, an enteric coating and a moisture resistant coating besides the core.

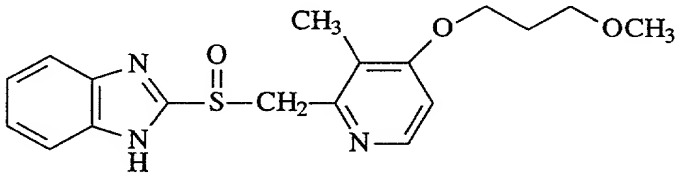
The moisture resistant coating is effective not only for the benzimidazole type compound but also for a drug whose decomposition is observed to be accelerated both in the presence of water and upon contact with gastric acid. That is, the present invention relates to a pharmaceutical preparation

comprising a core coated with an enteric coating and further with a moisture resistant coating, said core comprising a drug incorporated into it and the drug both being accelerated to be decomposed in the presence of water and being chemically unstable in gastric acid.

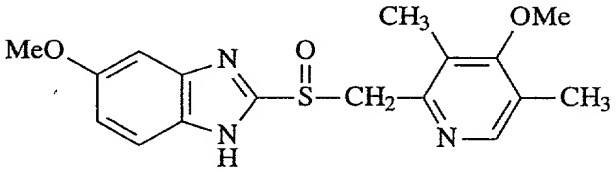
Further, the present invention relates to a pharmaceutical preparation comprising a core coated with an intermediates coating, further with an enteric coating and then with a moisture resistant coating, said core comprising a drug incorporated into it and the drug both being accelerated to be decomposed in the presence of water and being chemically unstable in gastric acid.

In the present invention, the benzimidazole type compounds or alkali metal salts thereof include e.g. rabeprazole, omeprazole, pantoprazole and lansoprazole, or sodium or potassium salts thereof. The structural formulae of these compounds are shown in formula 3.

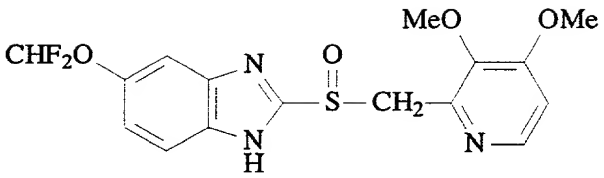
Formula 3



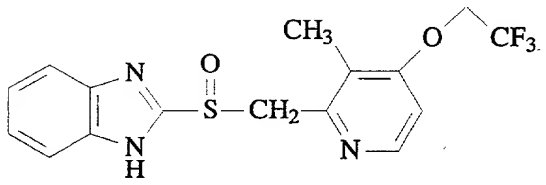
Rabeprazole



Omeprazole



Pantoprazole



Lansoprazole

Hereinafter, the benzimidazole type compound or an alkali metal salt thereof is collectively referred to as benzimidazole type compound.

The benzimidazole type compound in the present invention can be produced in a known method. For example, the compound can be produced by any methods disclosed in JP-A 52-62275, JP-A 54-141783, JP-A 1-6270 etc.

Sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide and hydroxypropyl cellulose in the present invention are mentioned in the Japanese Pharmacopoeia, and these are commercially available and easily obtainable. Aminoalkyl methaacrylate copolymer E, which is mentioned in the standards of non-medicines in the Japanese Pharmacopoeia, can be easily obtained. Further, crospovidone is a substance mentioned in the standards of pharmaceutical additives, and its commercial products of various grades with varying particle diameters are easily available, and their particle diameters can be regulated as necessary by a grinding device such as hammer

mill.

The blending ratio of the benzimidazole type compound to at least one selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone is 0.01 to 20 parts by weight, preferably 0.01 to 10 parts by weight, more preferably 0.1 to 10 parts by weight in total, to 1 part by weight of the benzimidazole type compound. In the present invention, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone can be used alone or 2 or more of these additives can be used in combination. Among these, it is effective to incorporate sodium hydroxide, potassium hydroxide and/or sodium carbonate into the benzimidazole type compound and it is more effective to incorporate 1) crospovidone and 2) sodium hydroxide, potassium hydroxide and/or sodium carbonate into the benzimidazole type compound. The blending ratio of a combination of these additives is 0.01 to 20 parts by weight to 1 part by weight of the benzimidazole type compound, and preferably the ratio of crospovidone is 0.5 to 5 parts by weight, and the ratio of sodium hydroxide, potassium hydroxide and/or sodium carbonate is 0.01 to 2 parts by weight.

The benzimidazole type compound when decomposed during storage under heating and humid conditions is observed to undergo significant coloring changes in particular. The

composition and/or the pharmaceutical preparation of the invention comprising the above-described various additives incorporated into it possesses the particularly outstanding effect of not only improving the stability of the ingredients but also inhibiting the coloring changes.

Conventionally used excipients such as lactose and mannitol can be used to prepare a pharmaceutical preparation by use of the invented composition comprising the benzimidazole type compound and at least one substance selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone incorporated thereto. Preferably, hydroxypropyl cellulose is used as a binder and crospovidone is used as a disintegrating agent.

It is known that crospovidone used generally as a disintegrating agent, when finely ground, can reduce the disintegrating force and swelling force inherent in the original disintegrating agent. Finely ground crospovidone having small particle diameters is used as a stabilizer for the benzimidazole type compound in the present invention, and it can be added in a larger amount than the amount of a usual disintegrating agent (usually 10 % or less). The average particle diameter of crospovidone is several μm to 50 μm, more preferably 4 μm to 50 μm.

Accordingly, the crospovidone used in the composition or in the pharmaceutical preparation according to the present

invention is preferably crospovidone having small average particle diameters of several μm to 50 μm, preferably 4 μm to 50 μm. As a matter of course, finely ground crospovidone and usual crospovidone may be used in combination.

The crospovidone, though varying depending on manufacturer and lot number, often contains a slight amount of peroxides as impurities. The benzimidazole type compound is inherently liable to oxidation so that when blended along with crospovidone, it may contain an antioxidant.

The antioxidant includes, but is not limited to, sodium sulfite, sodium pyrosulfite, vitamin E, rongalite, thioglycerol, sodium thiosulfate, ascorbate and acetyl cysteine.

Further, the present invention relates to a pharmaceutical preparation comprising a core which comprises at least one substance selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone incorporated into a benzimidazole type compound represented by formula 1, coated with an enteric coating. In the present invention, the term "core" refers to tablets, granules etc. Further, the present invention encompasses a pharmaceutical preparation comprising a core coated with an enteric coating, said core comprising a benzimidazole type compound and at least one selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E,

arginine aspartate, hydroxypropyl cellulose and crospovidone laminated therein or coated thereon with spherical granules consisting, as seed granules, of refined white sugar, a mixture of white sugar and starch, or crystalline cellulose etc. The benzimidazole type compound is very unstable under acidic conditions, so when administered, the benzimidazole type compound is decomposed immediately in contact with gastric acid in the stomach, to lose its physiological activity. Accordingly, it should be formed as a pharmaceutical preparation not dissolved in the stomach, that is, a pharmaceutical preparation having a benzimidazole type compound-containing core coated with an enteric substance in order to prevent it from being decomposed in the stomach.

Further, the present invention relates to a pharmaceutical preparation comprising a core coated with an intermediate coating and further with an enteric coating, said core comprising at least one substance selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone incorporated into a benzimidazole type compound represented by formula 1. Since the enteric coating is made generally of an acidic substance, its direct contact with the benzimidazole type compound is not preferable. Accordingly, an inert intermediate coating can be provided between the core comprising a benzimidazole type compound and the enteric coating. The term "inert" refers to a substance not adversely

affecting the stability of the benzimidazole type compound. The inert intermediate coating may be made of a water-soluble polymer, a water-soluble or water-disintegrating substance or a water-insoluble substance, and specific examples include hydroxypropyl cellulose, hydroxypropylmethyl cellulose, aminoalkyl methaacrylate copolymer E, lactose, mannitol, starch, crystalline cellulose, ethyl cellulose, vinyl acetate etc. When an intermediate coating made of a water-insoluble substance is applied, water-insoluble fine particles may be mixed in the coating, as disclosed in JP-A 1-290628.

In the present invention, the above-described pharmaceutical preparation coated with an enteric coating may be coated with a moisture resistant coating. The moisture resistant coating is a coating for inhibiting the passage of steam, and it is functionally a coating which in itself inhibits the transmission of steam or a coating which captures steam in the coating to inhibit the inflow of steam into the inside.

The moisture resistant coating possesses the function of defending the preparation against invasion of water into the benzimidazole type compound to improve its stability while preventing the cracking and deformation of tablets originating from the swelling of finely ground crospovidone upon moisture absorption.

The moisture resistant coating may be either a water-soluble coating or a water-insoluble coating, and this coating includes, but is not limited to, a coating consisting of e.g. polyvinyl acetal diethyl aminoacetate, HA Sankyo (a mixture of

polyvinyl acetal diethyl aminoacetate, hydroxypropylmethyl cellulose, stearic acid and fumaric acid), polyvinyl alcohol etc., a coating comprising at least one of cellulose derivatives such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose and ethyl cellulose incorporated into it, and/or a sugar coating based on white sugar.

The moisture resistant coating is useful not only for the benzimidazole type compound but also for a pharmaceutical preparation containing a drug having similar chemical properties. That is, its effect is observed to be significant when it is applied onto a pharmaceutical preparation containing a drug whose decomposition is observed to be accelerated both in the presence of water and upon contact with gastric acid.

That is, the present invention relates to a pharmaceutical preparation comprising a core which comprises a drug incorporated into it, the drug both being accelerated to be decomposed in the presence of water and being chemically unstable in gastric acid, coated with an enteric coating and further with a moisture resistant coating. Further, an intermediate coating may be coated between the enteric coating and the moisture resistant coating.

In the present invention, the effect is particularly outstanding where the benzimidazole type compound shown in formula 1 is rabeprazole.

That is, the present invention relates to a composition comprising sodium hydroxide, potassium hydroxide and/or sodium carbonate incorporated preferably into rabeprazole shown in

formula 3 or an alkali metal salt thereof.

Further, the present invention relates to a composition comprising 1) crospovidone and 2) sodium hydroxide, potassium hydroxide and/or sodium carbonate incorporated preferably into rabeprazole shown in formula 3 or an alkali metal salt thereof.

As described above, the crospovidone used is preferably finely ground until its average particle diameter is decreased to several μm to 50 μm. Further, an antioxidant may be added to prevent the influence of trace peroxides contained in crospovidone, as described above. Accordingly, an antioxidant may be incorporated into the composition comprising 1) crospovidone and 2) sodium hydroxide, potassium hydroxide and/or sodium carbonate incorporated into rabeprazole or an alkali metal salt thereof.

The present invention relates further to a pharmaceutical preparation comprising a core which comprises 1) crospovidone and 2) sodium hydroxide, potassium hydroxide and/or sodium carbonate incorporated preferably into rabeprazole shown in formula 3 or an alkali metal salt, coated with an enteric coating.

The present invention relates further to a pharmaceutical preparation comprising a core which comprises 1) crospovidone and 2) sodium hydroxide, potassium hydroxide and/or sodium carbonate incorporated preferably into rabeprazole shown in formula 3 or an alkali metal salt, coated with an intermediate coating and further with an enteric coating.

The present invention relates further to a pharmaceutical

preparation comprising a core which comprises 1) crospovidone and 2) sodium hydroxide, potassium hydroxide and/or sodium carbonate incorporated preferably into rabeprazole shown in formula 3 or an alkali metal salt, coated with an intermediate coating, further with an enteric coating and then with a moisture resistant coating.

The composition or the pharmaceutical preparation according to the present invention can be produced by any conventionally used processes.

For example, at least one selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone is incorporated into a benzimidazole type compound or an alkali metal salt thereof, then excipients are added thereto, and the mixture granulated in a dry or wet granulating process, followed by adding a disintegrating agent such as crospovidone as necessary and subsequently tabletting the granules whereby the composition or the pharmaceutical preparation of the invention can be produced. Alternatively, for example, at least one substance selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone is incorporated at high density into a benzimidazole type compound or an alkali metal salt to prepare benzimidazole-containing granules, while placebo granules not containing the benzimidazole type compound are separately

prepared, and then both the granules are mixed followed by adding a disintegrating agent such as crospovidone as necessary and subsequently tabletting the granules. As a matter of course, these processes are non-limiting examples.

In a concrete example, e.g. 100 g sodium rabeprazole as the benzimidazole type compound, 30 g sodium carbonate and 130 g mannitol are mixed, and hydroxypropyl cellulose dissolved in ethanol is gradually added to the mixture under stirring, followed by granulation, drying and screening through a 24-mesh screen. 30 g crospovidone and 2 g calcium stearate are added thereto, mixed and tabletted whereby tablets each weighing 135 mg can be obtained.

These tablets are sprayed by using a fluidized-bed granulator with a solution of hydroxypropyl cellulose in ethanol and further with a solution of hydroxypropylmethyl cellulose phthalate or an enteric methaacrylate copolymer in water/ethanol whereby enteric tablets provided with an intermediate coating can be produced.

According to the present invention, it is possible to stabilize the very unstable benzimidazole type compound. Examples of this effect are shown below.

Experimental Examples

50 mg sodium rabeprazole and 450 mg additives shown in the table below were mixed in a mortar.

The mixture was introduced into a transparent glass vial and stored in a cold place or at 60 °C or 40 °C under 75 % relative humidity for 1 week and their content was determined by high

performance liquid chromatography. Assuming that the content of the sample stored in the cold place is 100 %, the degrees of the residual content under the respective conditions are shown in Tables 1 through 3. Further, their coloring changes were visually evaluated. The sodium rabeprazole used was amorphous in Table 1 and crystalline in Tables 2 and 3. In Table 1, low-substituted hydroxypropyl cellulose (expressed as L-HPC) used as a disintegrating agent in addition to amorphous sodium rabeprazole was blended in the control; in Table 2, a sample further incorporating aluminum hydroxide (expressed as $Al(OH)_3$ in the table) i.e. an alkaline inorganic salt used as an antacid agent was used; and in Table 3, a sample incorporating polyvinyl pyrrolidone (expressed as PVP in the table) was used as a binder.

Table 1 Compatibility Test of Sodium Rabeprazole

		60°C	40°C-75%RH
Control	sodium rabeprazole (amorphous)	99.1	93.9
	sodium rabeprazole + L-HPC	80.4	73.3
The present application	sodium rabeprazole + crospovidone	98.1	90.4

Unit : %

Table 2 Compatibility Test of (crystalline) Sodium Rabeprazole

		60°C	40°C-75%RH
Control	sodium rabeprazole (crystalline)	99.8	91.8
	sodium rabeprazole + L-HPC	62.2	75.0
	sodium rabeprazole + $Al(OH)_3$	36.9	26.2
The present application	sodium rabeprazole + crospovidone	93.3	89.5
	sodium rabeprazole + Na_2CO_3	99.1	90.3
	sodium rabeprazole + Arg·Asp	97.5	90.7

Unit : %

Table 3 Compatibility Test of (Crystalline) Sodium Rabeprazole

		60°C	40°C-75%RH
Control	sodium rabeprazole (crystalline)	97.3	86.9
	sodium rabeprazole + PVP	89.5	67.7
The present application	sodium rabeprazole + hydroxypropyl cellulose	92.0	86.9
	sodium rabeprazole + Na_2CO_3	93.0	82.8
	sodium rabeprazole + NaOH	91.6	98.8
	sodium rabeprazole + KOH	92.6	96.8
	sodium rabeprazole + Eudragit E	102.4	86.0
	sodium rabeprazole + K_2CO_3	104.5	81.3

Unit : %

Any coloring changes of the blended samples according to the present invention were lower than those of the controls. Further, it is evident from the results of content stability in Tables 1 through 3 that the ingredients used in the present invention, that is, sodium carbonate (expressed as Na_2CO_3 in the table), sodium carbonate (expressed as K_2CO_3 in the table), sodium hydroxide (expressed as NaOH in the table), potassium hydroxide (expressed as KOH), aminoalkyl methaacrylate copolymer E (expressed as Eudragit E®), arginine · aspartate (expressed as Arg · Asp in the table), hydroxypropyl cellulose and crospovidone stabilize the benzimidazole type compound.

Effect of Sodium Carbonate in Tablets

Tablets containing different amounts of sodium carbonate, obtained in Examples 4 to 9 shown below, were stored at 40 °C under 75 % relative humidity for 1 week, and the contents of sodium rabeprazole in the tablets as determined by high performance liquid chromatography were shown in Table 4.

Table 4

Stability Evaluation of Tablet Formulations by Wet Granulation

Formulation	Ex.4	Ex.5	Ex.6	Ex.7	Ex.8	Ex.9
(1week)						
cold place	99.4	99.0	98.7	99.4	99.5	98.9
40°C-75%RH	83.8	85.7	85.1	92.5	92.8	95.5
(1month)						
cold place	99.7	99.7	99.7	99.7	99.7	99.6
25°C-75%RH	97.8	98.5	98.3	99.2	99.3	99.3

Unit : %

Because the stability of the content of sodium rabeprazole in the tablets is improved depending on the amount of sodium carbonate added, the effect of sodium carbonate added in the present invention is evident.

Effect of Crospovidone in Tablets

Tablets containing different amounts of crospovidone powder, obtained in Examples 10 to 12 shown below, were stored at 40 °C under 75 % relative humidity for 1 week, and the contents of sodium rabeprazole in the tablets as determined by high performance liquid chromatography were shown in Table 5. The tablets were subject to less coloring change as the amount of the crospovidone powder added was increased.

Table 5

Stability of Crospovidone-Added Tablets by Wet Granulation

Formulation	Ex.10	Ex.11	Ex.12
(1week)			
cold place	99.7	99.7	99.7
40°C-75%RH	97.8	98.5	98.3
(1month)			
cold place	99.4	99.0	98.7
40°C-75%RH	83.8	85.7	85.1

Unit : %

It is evident that the stability of the benzimidazole type compound is improved by adding crospovidone.

Effect of Finely Ground Crospovidone in Tablets

Tablets containing crospovidone having a different average particle diameter, obtained in Examples 16 to 18 shown below, were stored in a cold place or at 25 °C under 75 % relative humidity for 1 month and then evaluated for their thickness to evaluate the ratio of swelling of the tablets stored at 25 °C under 75 % relative humidity to swelling of the tablets stored in the cold place. The results were that the ratios of swelling of the tablets containing crospovidone having average particle diameters of 51 μm, 12 μm and 6 μm were 1.61, 1.48 and 1.43, respectively.

As crospovidone is made fine powder having a small average particle diameter, the ratio of the swelling of the tablets is decreased. Therefore, the cracking or deformation resulting from the swelling of the tablets is reduced. Accordingly, it is evident that the particle size reduction of crospovidone contributes to improvement of stability of tablets.

Effect of a Moisture Resistant Coating Applied onto Tablets Coated with an Enteric Coating

Tablets coated with an enteric coating and tablets coated with both an enteric coating and a moisture resistant coating, obtained in Examples 19 to 20 shown below, were stored at 25 °C under 75 % relative humidity for 1 week, and the content of a rabeprazole analogue in the tablets was determined by high performance liquid chromatography. The results indicated that

the contents of the rabeprazole analogue in the tablets coated with an enteric coating and the tablets coated with both an enteric coating and a moisture resistant coating were 2.38 % and 2.23 %, respectively.

It is evident that the tablets coated with both an enteric coating and a moisture resistant coating possess stability equal to or higher than that of the tablets coated with an enteric coating.

Placebo tablets obtained in Examples 21 to 23 shown below were stored in a cold place or at 40 °C under 75 % relative humidity for 1 week and then evaluated for their thickness to evaluate the ratio of swelling of the tablets stored at 40 °C under 75 % relative humidity to swelling of the tablets stored in the cold place. The results indicated that the ratios of swelling of the tablets coated with an enteric coating, tablets prepared by coating said enteric coating-coated tablets with a moisture resistant coating, and tablets prepared by coating said enteric coating-coated tablets with a moisture resistant coating consisting of HA (Sankyo) (i.e., a mixture of polyvinyl acetal diethyl aminoacetate, hydroxypropylmethyl cellulose, macrogol and talc) were 1.15, 1.03 and 1.12, respectively.

Since the degree of swelling of the tablets coated with both an enteric coating and a moisture resistant coating is smaller during storage than that of the tablets coated with an enteric coating only, it is evident that the stability in shape of the tablets is improved.

Effect of an Antioxidant Added to the Portion of a Core

Containing the Benzimidazole Type Compound

Tablets containing a different amount of a peroxide, obtained in Examples 24 to 26 shown below, were measured for the content of a sodium rabeprazole analogue by high performance liquid chromatography. The results indicate that the amounts of the initial rabeprazole analogue in the tablets incorporating crospovidone containing 18 ppm, 190 ppm and 310 ppm peroxide were 0.65 %, 0.88 % and 1.13 % respectively, indicating that as the amount of the peroxide in crospovidone is increased, the decomposition of sodium rabeprazole is promoted to increase the amount of the analogue.

Further, 1 g crospovidone containing 201 ppm peroxide was accurately taken, and sodium sulfite (amounts: 4 levels i.e. no addition, 0.02 %, 0.05 % and 0.10 %) was added thereto and mixed well, and the amount of the peroxide in the mixture was determined according to a test method described in the Japanese Pharmacopoeia. The results indicated that the amounts of the peroxide in the compositions wherein the amounts of sodium sulfite added were none, 0.02 %, 0.05 % and 0.10 %, were 201 ppm, 184 ppm, 108 ppm, and 0 ppm respectively, indicating that as the amount of sodium sulfite added was increased, the amount of the peroxide was reduced.

From the foregoing, it is evident that the stability of the benzimidazole type compound in a pharmaceutical preparation is improved by adding the antioxidant to the portion of cores in tablets containing the benzimidazole type compound and crospovidone.

Examples

Hereinafter, the present invention is described more in detail by reference to Examples, which however are not intended to limit the present invention.

Example 1

10 g sodium carbonate and 100 g mannitol were added to and mixed with 10 g sodium rabeprazole, and 2.5 g hydroxypropyl cellulose dissolved in ethanol was gradually added to the mixture under stirring to make granules which were dried and screened followed by adding calcium stearate and tabletting to give tablets each weighing 120 mg containing 10 mg sodium rabeprazole.

Example 2

The tablets obtained in Example 1 were sprayed by using a fluidized-bed granulator with a solution of 10 g hydroxypropylmethyl cellulose phthalate dissolved in a mixed solvent of water and ethanol (2 : 8), to produce enteric tablets.

Example 3

The tablets obtained in Example 1 were sprayed by using a fluidized-bed granulator with a solution of hydroxypropylmethyl cellulose in ethanol, to produce enteric tablets in the same manner as in Example 2.

Examples 4 to 9

0 to 10 g sodium carbonate and 15 to 90 g mannitol were added to and mixed with 10 g sodium rabeprazole, and 0.7 to 2 g hydroxypropyl cellulose dissolved in ethanol was gradually added to the mixture to make granules under stirring in a wet

granulation process, thus preparing the active granules. Separately, 2 g hydroxypropyl cellulose dissolved in ethanol was gradually added to 100 g mannitol to produce granules under stirring in a wet process to prepare placebo granules. Then, the main-drug granules were mixed with the placebo granules, and 5 % crospovidone and a slight amount of magnesium stearate were added thereto in a powdery form and tabletted to give tablets each weighing 100.5 mg containing 10 mg sodium rabeprazole. Each formulation is shown in Table 6.

Table 6 Tablet Formation by Wet Granuration

	Formulation	Ex.4	Ex.5	Ex.6	Ex.7	Ex.8	Ex.9
Active granule	sodium rabeprazole	10.0	10.0	10.0	10.0	10.0	10.0
	anhydrous sodium carbonate	-	-	-	5.0	5.0	10.0
	mannitol	82.0	30.0	20.0	25.0	15.0	20.0
	hydroxypropyl cellulose	2.0	1.0	0.7	1.0	0.7	1.0
	(sub-total)	94.0	41.0	30.7	41.0	30.7	41.0
Placebo granule	mannitol	-	52.0	62.1	52.0	62.1	52.0
	hydroxypropyl cellulose	-	1.0	1.2	1.0	1.2	1.0
	(sub-total)	0.0	53.0	63.3	53.0	63.3	53.0
Powder added	crospovidone	5.0	5.0	5.0	5.0	5.0	5.0
	magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
	(sub-total)	6.5	6.5	6.5	6.5	6.5	6.5
	total	100.5	100.5	100.5	100.5	100.5	100.5

Unit:mg

Examples 10 to 12

Tablets were obtained in the same manner as in Examples 4 to 9 except that the amounts of crospovidone powder added were 3 levels, that is, 0, 2.5, and 5 %. Each formulation is shown in Table 7.

Table 7

Formulation of Crospovidone-Added Tablets by Wet Granulation

	Formulation	Ex.10	Ex.11	Ex.12
Active granule	sodium rabeprazole (crystalline)	10.0	10.0	10.0
	anhydrous sodium carbonate	5.0	5.0	5.0
	mannitol	25.0	25.0	25.0
	hydroxypropyl cellulose	1.0	1.0	1.0
	(sub-total)	41.0	41.0	41.0
Placebo granule	mannitol	56.9	54.4	52.0
	hydroxypropyl cellulose	1.1	1.1	1.0
	(sub-total)	58.0	55.5	53.0
Powder added	crospovidone	-	2.5	5.0
	magnesium stearate	1.5	1.5	1.5
	(sub-total)	1.5	4.0	6.5
	total	100.5	100.5	100.5

Unit:mg

Examples 13 to 14

According to the 2 formulations shown in Table 8, 0 to 50 g sodium carbonate, 79.3 to 84.3 g mannitol, 4.2 g crospovidone and 1.5 g magnesium stearate were added to 10 mg sodium rabeprazole, mixed well, and directly tabletted to give tablets each weighing 100 mg containing 10 mg sodium rabeprazole.

Table 8

Tablet Formulation by Direct Tabletting

Formulation	Ex.13	Ex.14
sodium rabeprazole (crystalline)	10.0	10.0
anhydrous sodium carbonate	-	5.0
mannitol	84.3	79.3
crospovidone	4.2	4.2
magnesium stearate	1.5	1.5
total	100.0	100.0

Unit:mg

Example 15

50 g sodium carbonate and 2 g magnesium stearate were added to 100 g sodium rabeprazole, mixed well to make granules under dry compression granulation process, to prepare main-drug granules. Separately, 76.3 g mannitol was added to and mixed well with 4.2 g crospovidone, and 2.3 g hydroxypropyl cellulose dissolved in ethanol was gradually added thereto to make granules under stirring in a wet process to prepare placebo granules. Then, the main-drug granules were mixed with the placebo granules, and a slight amount of magnesium stearate was added thereto in a powdery form and tabletted to give tablets each weighing 100 mg containing 10 mg sodium rabeprazole as shown in Table 9.

Table 9

Tablet Formulation by Dry Granulation

Formulation		Ex.15
Active granule	sodium rabeprazole (crystalline)	10.0
	anhydrous sodium carbonate	5.0
	magnesium stearate	0.2
	(sub-total)	15.2
Placebo granule	mannitol	76.8
	crospovidone	4.2
	hyroxypropyl cellulose	2.3
	(sub-total)	83.3
Powder added	magnesium stearate	1.5
	total	100.0

Unit:mg

Examples 16 to 18

527 g crospovidone having a different average particle diameter and 20 g hydroxypropyl cellulose were mixed with 100 g sodium rabeprazole, and 3 g magnesium stearate was added thereto in a powdery form, followed by tabletting to give tablets each weighing 65 mg containing 10 mg sodium rabeprazole as shown in Table 10. Crospovidone used is a product of BASF Ltd., and its average diameter is 51 μm for Colidone CL™, 12 μm for Colidone CLM™ and 6 μm for a hammer mill-ground product of Colidone CLM™.

Table 10

Formulations Containing Crospovidone having Different Particle Diameters

Formulation	Ex.16	Ex.17	Ex.18
sodium rabeprazole	10.0	10.0	10.0
crospovidone (colidone CL)	52.7	-	-
crospovidone (colidone CLM)	-	52.7	-
crospovidone (ground product of colidone CLM)	-	-	52.7
hydroxypropyl cellulose	2.0	2.0	2.0
magnesium stearate	0.3	0.3	0.3
(sub-total)	65.0	65.0	65.0

Unit:mg

Note: Average diameters

Crospovidone (Colidone CL): 51 μm

Crospovidone (Colidone CLM): 12 μm

Crospovidone (ground product of Colidone CLM): 6 μm

Examples 19 to 20

The portion of a core containing sodium rabeprazole was granulated with ethanol and coated with a water-insoluble intermediate coating containing ethyl cellulose, crospovidone and magnesium stearate. Further, the resulting granules were coated with a coating to give tablets coated with an enteric coating or with both an enteric coating and a moisture resistant coating. The formulation is shown in Table 11.

Table 11

Formulation of a Pharmaceutical Preparation Having an Enteric Coating and a Moisture Resistant Coating Applied Thereon

	Formulation	Ex.19	Ex.20
Core	sodium rabeprazole	10.0	10.0
	mannitol	36.2	36.2
	crospovidone	15.6	15.6
	sodium hydroxide	0.1	0.1
	anhydrous sodium carbonate	5.0	5.0
	hydroxypropyl cellulose	2.0	2.0
	magnesium stearate	1.1	1.1
	(sub-total)	70.0	70.0
Intermediate coating	ethyl cellulose	0.5	0.5
	crospovidone	1.0	1.0
	magnesium stearate	0.1	0.1
	(sub-total)	1.6	1.6
Enteric coating	hydroxypropyl cellulose cellulose phthalate	8.0	8.0
	monoglyceride	0.8	0.8
	talc	0.75	0.75
	titanium oxide	0.4	0.4
	yellow iron oxide	0.05	0.05
	(sub-total)	10.0	10.0
Moisture resistant coating	hydroxypropylmethyl cellulose	-	3.0
	macrogol	-	0.6
	talc	-	1.4
	(sub-total)		5.0
total		81.6	86.6

Unit:mg

Examples 21 to 23

As placebo tablets not containing the benzimidazole type compound, tablets having a water-soluble intermediate layer of hydroxypropyl cellulose applied onto the portion of cores therein were prepared. The tablets were coated further with

an enteric coating to prepare tablets coated with an enteric coating, and further the enteric coating-coated tablets were sprayed with white sugar or HA (Sankyo) to prepare tablets coated with a moisture resistant coating. The formulation is shown in Table 12.

Table 12

Placebo Formulation

	Formulation	Ex.21	Ex.22	Ex.23
Core	mannitol	31.8	31.8	31.8
	crospovidone (colidone CLM)	27.7	27.7	27.7
	hydroxypropyl cellulose	5.0	5.0	5.0
	magnesium stearate	0.5	0.5	0.5
	(sub-total)	65.0	65.0	65.0
Intermediate coating	hydroxypropyl cellulose	3.0	3.0	3.0
Enteric coating	hydroxypropylmethyl cellulose phthalate	8.0	8.0	8.0
	monoglyceride	0.8	0.8	0.8
	talc	0.75	0.75	0.75
	titanium oxide	0.4	0.4	0.4
	yellow iron oxide	0.05	0.05	0.05
	(sub-total)	10.0	10.0	10.0
Moisture resistant coating	white sugar	-	10.0	-
	HA (Sankyo)*	-	-	10.0
total		78.0	88.0	88.0

Unit:mg

Note: HA (Sankyo)*

A mixture of polyvinyl acetal diethyl aminoacetate, hydroxypropylmethyl cellulose, Macrogol and talc.

Examples 24 to 26

Tablets containing crospovidone with different contents of sodium rabeprazole and a peroxide, sodium hydroxide and sodium carbonate were obtained by granulation in a wet process,

according to the formulation in Table 13.

Table 13

Formulation Containing Crospovidone with Different Contents of Peroxide

Formulation	Ex.24	Ex.25	Ex.26
sodium rabeprazole	10.0	10.0	10.0
mannitol	36.9	36.9	36.9
crospovidone (INF-10)*1	14.0	-	-
crospovidone (INF-10)*2	-	14.0	-
crospovidone (colidone CLM)*3	-	-	14.0
crospovidone (colidone CL)	14.0	14.0	14.0
sodium hydroxide	0.5	0.5	0.5
anhydrous sodium carbonate	2.5	2.5	2.5
hydroxypropyl cellulose	2.0	2.0	2.0
magnesium stearate	1.1	1.1	1.1
(total)	70.0	70.0	70.0

Unit:mg

Note:

Crospovidone (INF-10)*1: (peroxide content: 18 ppm)

Crospovidone (INF-10)*2: (peroxide content: 190 ppm)

Crospovidone (Colidone CLM)*3: (peroxide content: 310 ppm)

Example 27

43.5 g finely ground crospovidone and 6 g hydroxypropyl cellulose were added to 30 g sodium rabeprazole, mixed well, and then a solution of sodium hydroxide in ethanol (solution of 1.5 g sodium hydroxide dissolved in ethanol) was gradually added to the mixture under stirring to make granules, followed by drying and subsequent regulation of the size of granules in a small type speed mill. 3 % crospovidone and 1.6 % magnesium stearate were added to the regulated granules, mixed and

tabletted into tablets each weighing 70 mg containing 10 mg sodium rabeprazole.

Example 28

The tablets obtained in Example 27 were coated by using a fluidized-layer granulator with a hydrous ethanol solution containing hydroxypropyl cellulose and a slight amount of magnesium stearate, to give tablets having 2 mg intermediate coating laminated thereon. Then, the tablets coated with the intermediate coating were sprayed by using a fluidized-layer granulator with a hydrous ethanol solution containing hydroxypropyl cellulose phthalate, monoglyceride, talc and titanium oxide, to give enteric tablets coated with 10 mg enteric coating.

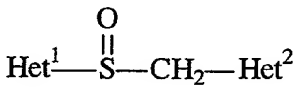
Example 29

The enteric tablets obtained in Example 28 were sprayed by using a fluidized-layer granulator with purified water containing hydroxypropylmethyl cellulose, Macrogol 6000™ and talc to give tablets coated with 5 mg moisture resistant coating.

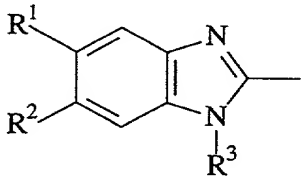
Claims

1. A pharmaceutical composition comprising (A) benzimidazole compound represented by the following structural formula (formula 1) or an alkali metal salt thereof and (B) at least one selected from the group consisting of sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone.

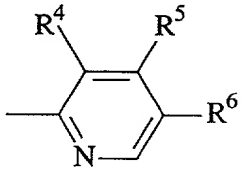
Formula 1



In the formula 1, Het^1 is



Het^2 is



R^1 and R^2 are the same as or different from each other and are selected from a hydrogen, a methoxy and a difluoromethoxy, R^3 is selected from a hydrogen and a sodium, R^4, R^5 and R^6 are the same as or different from each other and are selected from hydrogen, methyl, methoxy, methoxypropoxy and

trifluoroethoxy.

2. The composition according to Claim 1, wherein the benzimidazole compound is rabeprazole, omeprazole, pantoprazole or lansoprazole.

3. The composition according to Claim 1, which comprises 1 part by weight of (A) and 0.01 to 20 parts by weight of (B).

4. A pharmaceutical preparation comprising a core consisting of the composition as claimed in Claim 1 and an enteric coating.

5. A pharmaceutical preparation comprising a core consisting of the composition as claimed in Claim 1, an intermediate coating and an enteric coating.

6. A pharmaceutical preparation comprising a core consisting of the composition as claimed in Claim 1, an intermediate coating, an enteric coating and a moisture resistant coating.

7. The composition according to Claim 1, wherein (A) is rabeprazole and an alkali metal salt thereof and (B) is at least one selected from the group consisting of sodium hydroxide, potassium hydroxide and sodium carbonate.

8. The composition according to Claim 1, wherein (A) is rabeprazole or an alkali metal salt thereof and (B) is (1) crospovidone and at least one selected from the group consisting of (2) sodium hydroxide, potassium hydroxide and sodium carbonate.

9. A pharmaceutical preparation comprising a core consisting of the composition as claimed in Claim 8 and an

enteric coating.

10. A pharmaceutical preparation comprising a core consisting of the composition as claimed in Claim 8, an intermediate coating and an enteric coating.

11. A pharmaceutical preparation comprising a core consisting of the composition as claimed in Claim 8, an intermediate coating, an enteric coating and a moisture resistant coating.

12. The composition according to claim 8, which further comprises an antioxidant.

13. The pharmaceutical preparation according to any of Claims 9 to 11, wherein the core further comprises an antioxidant.

14. A pharmaceutical preparation comprising a core which comprises a drug incorporated into it and the drug being accelerated to be decomposed in the presence of water and being chemically unstable in gastric acid, coated with an enteric coating and further with a moisture resistant coating.

15. A pharmaceutical preparation comprising a core which comprises a drug incorporated into it and the drug being accelerated to be decomposed in the presence of water and being chemically unstable in gastric acid, coated with an intermediate coating, further with an enteric coating and then with a moisture resistant coating.

Abstract

The present invention provides a chemically stable pharmaceutical preparation of a benzimidazole type compound. That is, the present invention relates to a composition comprising at least one substance selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone incorporated into a benzimidazole type compound or an alkali metal salt thereof.

Case No. _____

Nixon & Vanderhye P.C. (12/97)

RULE 63 (37 C.F.R. 1.63)
DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Stabilized composition comprising a benzimidazole type compound

the specification of which (**check applicable box(s)**):

☐ is attached hereto
☐ was filed on _____ as U.S. Application Serial No. _____
☒ was filed as PCT international application No. PCT/JP99/02098 on April 20, 1999
and (if applicable to U.S. or PCT application) was amended on _____

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with 37 C.F.R. 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed or, if no priority is claimed, before the filing date of this application:

Priority Foreign Application(s):

Application Number	Country	Day/Month/Year Filed
10-109288	Japan	20/04/1998

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

Application Number	Date/Month/Year Filed

I hereby claim the benefit under 35 U.S.C. 120/365 of all prior United States and PCT international applications listed above or below and, insofar as the subject matter of each of the claims of this application is not disclosed in such prior applications in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose material information as defined in 37 C.F.R. 1.56 which occurred between the filing date of the prior applications and the national or PCT international filing date of this application:

Prior U.S./PCT Application(s):

Application Serial No.	Day/Month/Year Filed	Status: patented pending, abandoned

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon. And I hereby appoint **NIXON & VANDERHYE P.C., 1100 North Glebe Rd., 8th Floor, Arlington, VA 22201-4714, telephone number (703) 816-4000 (to whom all communications are to be directed)**, and the following attorneys thereof (of the same address) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent: Arthur R. Crawford, 25327; Larry S. Nixon, 25640; Robert A. Vanderhye, 27076; James T. Hosmer, 30184; Robert W. Faris, 31352; Richard G. Besha, 22770; Mark E. Nusbaum, 32348; Michael J. Keenan, 32106; Bryan H. Davidson, 30251; Stanley C. Spooner, 27393; Leonard C. Mitchard, 29009; Duane M. Byers, 33363; Jeffry H. Nelson, 30481; John R. Lastova, 33149; H. Warren Burnam, Jr., 29366; Thomas E. Byrne, 32205; Mary J. Wilson, 32955; J. Scott Davidson, 33489; Alan M. Kagen, 36178; William J. Griffin, 31260; Robert A. Molan, 29834; B. J. Sadoff, 36663; James D. Berquist, 34776; Updeep S. Gill, 37334.

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268050

Case No. _____ Nixon & Vanderhye P.C. (12/97)

RULE 63 (37 C.F.R. 1.63)
DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

4-00

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7. Inventor's Signature: Akira Kato Date: Jan. 14, 2000
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8. Inventor's Signature: Masao Kawamura Date: Jan. 14, 2000
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9. Inventor's Signature: Satoshi Fujioka Date: Jan. 12, 2000
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11. Inventor's Signature: _____ Date: _____
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Residence: (city) _____ (state/country) _____
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(Zip Code) _____

12. Inventor's Signature: _____ Date: _____
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